Arch. Pharm. Res.
DOI 10.1007/s12272-015-0641-4

RESEARCH ARTICLE

Asymmetric synthesis of H_1 receptor antagonist (*R*,*R*)-clemastine

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Received: 26 June 2015 / Accepted: 23 July 2015

Abstract The first asymmetric synthesis of (*R*,*R*)-clemastine (**1**) has been accomplished by the coupling of (*R*)-tertiary alcohol **2** and (*R*)-chloroethylpyrrolidine **3** via *O*-alkylation. (*R*)-Tertiary alcohol **2** was synthesized by stereoselective alkylation of chiral α-benzyloxy ketone with Grignard reagent via chelation-controlled 1,4-asymmetric induction. In the reaction, chiral benzyl group acts as a chiral auxiliary as well as a protecting group. (*R*)-Chloroethylpyrrolidine **3** was prepared by asymmetric transformation starting with L-homoserine lactone, in which racemization-minimized *N*-allylation and ring-closing metathesis were involved as key steps.

Keywords (*R*,*R*)-Clemastine · H_1 receptor antagonist · Asymmetric synthesis · Asymmetric transformation

Introduction

Clemastine (**1**) is a selective H_1-receptor antagonist with excellent antihistaminic activity (Nelson 2002). Clemastine has two chiral centers, and its (*R*,*R*)-form is the most active stereoisomer on the market. (Fig. 1) The chiral center at benzhydryl carbon has a significant influence on potency, while the chiral center in the pyrrolidine ring is of lesser importance. All stereoisomers of clemastine, including (*R*,*R*)-form, were prepared by the conventional optical resolution method (Ebnöther and Weber 1976; Takaoka 1978; Nikiforov et al. 1990). No asymmetric synthesis of (*R*,*R*)-clemastine has been described yet, although only one asymmetric synthesis of (*S*,*S*)-clemastine has been reported recently (Fournier et al. 2010).

We now report the first asymmetric synthesis of (*R*,*R*)-clemastine featuring a chelation-controlled diastereoselective alkylation and a RCM-mediated asymmetric transformation. Based on a general disconnection approach to ethers, (*R*)-tertiary alcohol **2** and (*R*)-chloroethylpyrrolidine **3** are required for the synthesis of optically active (*R*,*R*)-clemastine. It is envisioned that the chelation-controlled asymmetric alkylation process for 1,2-diols developed by us would permit the efficient synthesis of (*R*)-tertiary alcohol **2** (Jung and Kim 2007; Chang et al. 2008; Kim et al. 2014). In addition, we have also developed asymmetric transformation of L-homoserine lactone to 2-substituted pyrrolidines, which might provide a direct way to (*R*)-chloroethylpyrrolidine **3** (Kim et al. 2011).

Materials and methods

The melting points were obtained using MEL-TEMP® and were uncorrected. Optical rotations were measured on a JASCO DIP 1000 digital polarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian 400 spectrometer and the chemical shifts are reported as values in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. The infrared (IR) spectra were recorded on a JASCO FT/IR-430 spectrophotometer. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck precoated silica gel glass plates ($60F_{254}$). Column chromatography was performed using forced flow of the indicated solvent on Merck Kieselgel 60 (230–400 mesh). Unless otherwise noted, the materials were obtained from commercially available sources and were used without

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Published online: 29 July 2015

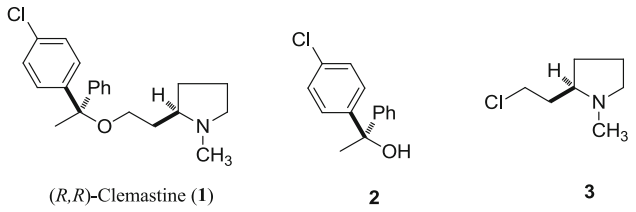


Fig. 1 (*R*,*R*)-Clemastine and its chiral intermediates

further purification. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl under an argon atmosphere. Benzene, dichloromethane, triethylamine (TEA) and xylene were freshly distilled under a nitrogen atmosphere with calcium hydride.

(*R*)-2-(1-Methylpyrrolidine-2-yl)ethanol (8)

To a suspension of lithium aluminum hydride (72 mg, 1.92 mmol) in THF (2 mL) was added a solution of carbamate **6** [105 mg, 0.56 mmol, $[\alpha]_D^{25}$ +4.73 (*c* 1.0, chloroform), 95 % ee] in THF (3 mL) dropwise at room temperature. The reaction mixture was stirred and refluxed for 2 h, then cooled, quenched with water (30 μL) and 15 % aqueous NaOH (20 μL), diluted with THF (20 mL), dried over anhydrous K_2CO_3, filtered on Celite, and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 1 % saturated ammonia water in methanol to give the title compound **8** as a colorless oil (53 mg, 73 %): IR (NaCl, neat): cm^{-1} 3375, 2947, 1455, 1057; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (br s, 1H), 4.01 (td, J = 10.8, 3.2 Hz, 1H), 3.68 (dt, J = 10.8, 3.2 Hz, 1H), 3.06 (m, 1H), 2.58 (m, 1 H), 2.36 (s, 3H), 2.15 (m, 1H), 2.00 (m, 1H), 1.88 (m, 4H), 1.50 (td, J = 10.8, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.2, 60.1, 56.9, 40.8, 31.2, 28.1, 23.1; $[\alpha]_D^{23}$ +74.9 (*c* 0.2, EtOH) {$[\alpha]_D$-78.9 (*c* 1.03, EtOH) for (*S*)-isomer (Fournier et al. 2010)}; LRMS (CI): m/z (relative intensity) 130 ($[M+H]^+$, 44 %); HRMS (CI) calcd. for $C_7H_{16}O$ $[M+H]^+$ 130.1232, found 130.1232.

(*R*)-2-(2-Chloroethyl)-1-methylpyrrolidine hydrochloride (3)

To a solution of (*R*)-2-(1-methylpyrrolidine-2-yl)ethanol (**8**, 95 % ee, 49 mg, 0.38 mmol) in chloroform (2 mL) was added dropwise thionyl chloride (0.1 mL) in chloroform (1 mL) at 0 °C. After being refluxed for 1 h, the resulting mixture was concentrated to dryness. The residue was triturated with MeOH, followed by addition of a small amount of charcoal. The mixture was refluxed for 1 h, filtered through Celite, and the filtrate was concentrated in vacuo to provide the title compound as a yellow solid (70 mg, 100 %). IR (KBr, disc): cm^{-1} 3417, 2957, 2647, 2505, 1636, 1457,1308,1033; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.5 (s, 1H), 3.89 (m, 2H), 3.58 (m, 1H), 3.41 (m, 1H), 2.91 (m, 1H), 2.87 (d, *J* = 5.2 Hz, 3H), 2.55 (m, 1H), 2.43 (m, 1H), 2.31 (m, 2H), 2.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.4, 56.1, 41.4, 39.4, 32.4, 29.2, 21.5. LRMS (FAB): m/z (relative intensity) 148 ($[M-Cl]^+$, 100 %).

The free base of (*R*)-**3** was obtained as a colorless oil by treatment with aqueous KOH, extraction with CH_2Cl_2, drying over Na_2SO_4, and concentrated in vacuo. The free base is used immediately without storage:

2-[(*R*)-[(4*R*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-(4-methoxyphenyl)methoxy]-1-phenylethanol (10)

A solution of alcohol **9** (100 mg, 0.42 mmol) in THF (3 mL) was added to a suspension of KH (280 mg, 35 % in oil, 0.63 mmol) in THF (3 mL). After being stirred at 55 °C for 30 min, styrene oxide (75.5 μL, 0.63 mmol) and 18-crown-6 ether (5 mg) were added at room temperature and the mixture was gradually heated to refluxing temperature for 24 h. The reaction mixture was quenched with aq. NH_4Cl (10 mL) and diluted with ethyl acetate (30 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The resulting crude residue was purified by column chromatography on silica gel (17 % ethyl acetate in hexane) to give the title compound **10** as an oil (38.4 mg, 39 %); IR (NaCl, neat): cm^{-1} 3443, 3031, 2960, 2927, 1455, 1258; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.16 (m, 5H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 4.81(dd, *J* = 9.6, 3.2 Hz, 1H), 4.32–4.26 (m, 1H), 4.20 (d, *J* = 8.0 Hz, 1H), 3.72 (s, 3H), 3.61–3.54 (m, 2H), 3.48 (dd, *J* = 8.8, 7.2 Hz, 1H), 1.42 (s, 3H), 1.33 (s, 3H). LRMS (FAB): m/z (relative intensity) 381 ($[M+Na]^+$, 52 %); HRMS (FAB) calcd. for $C_{21}H_{26}O_5Na$ $[M+Na]^+$ 381.1678, found 381.1676.

2-[(4*R*)-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-(*S*)-(4-methoxyphenyl)methoxy]-1-phenylethanone (11)

TPAP (18.9 mg, 0.054 mmol) was added to a mixture of alcohol **10** (192 mg, 0.54 mmol) and NMO (126 mg, 1.07 mmol) in dichloromethane (10 mL). After being stirred for 1 h at room temperature, the reaction mixture was quenched by the addition of saturated aqueous sodium sulfite solution (1 mL). The resulting mixture was diluted with dichloromethane. The organic layer was washed successively with brine, aqueous copper sulfate solution, water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The resulting crude residue was purified by column chromatography on silica gel (17 % ethyl acetate in hexane) to give the title compound **11** as a white solid (161 mg, 84 %); mp: 59–60 °C (recrystallization from the mixture of *n*-hexane and EtOAc); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.80 (d, 2H, $J = 8.0$ Hz), 7.78 (d, 2H, $J = 8.0$ Hz), 7.34 (t, 2H, $J = 7.6$ Hz), 7.19–7.17 (m, 1H), 6.47 (t, 1H, $J = 7.6$ Hz), 4.63 (d, 1H, $J = 16.4$ Hz), 4.57 (d, 1H, $J = 16.4$ Hz), 4.43–4.36 (m, 2H), 3.73 (s, 3H), 3.60 (dd, 1H, $J = 8.4$, 6.4 Hz), 3.51 (dd, 1H, $J = 8.4$, 6.4 Hz), 1.35 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.11, 159.79, 134.92, 133.51, 128.94, 128.69, 128.38, 127.78, 113.93, 109.98, 83.29, 78.84, 770.99, 65.91, 55.07, 26.45, 25.45; IR (KBr, disc): cm^{-1} 2980, 2927, 1698, 1610, 1584, 1513, 1450, 1240; $[\alpha]_D^{23}$ −86.6 (*c* 0.51, $CHCl_3$); LRMS (FAB): m/z (relative intensity) 379 ($[M+Na]^+$, 100 %); HRMS (FAB) calcd. for $C_{21}H_{24}O_5Na$ $[M+Na]^+$ 379.1521, found 379.1515.

(1*R*)-1-(4-Chlorophenyl)-2-{(1*S*)-[(4*R*)-(2,2-dimethyl-[1,3]-dioxolan-4-yl)]-(4-methoxyphenyl)methoxy}-1-phenylethanol (12)

A mixture of ketone **11** (126 mg, 0.35 mmol) and $MgBr_2$-OEt_2 (357 mg, 1.42 mmol, pre-dried with heat gun under vacuum) in CH_2Cl_2 (7 mL) was sonicated in ultrasonic cleaning water bath for 10 min, and then cooled to −78 °C. 4-Chlorophenylmagnesium bromide in diethyl ether solution (0.71 mL, 0.71 mmol, 1 M in Et_2O) was added dropwise to the mixture. After being stirred at −78 °C for 2 h, the mixture was allowed to warm to room temperature. The reaction mixture was quenched with aqueous $NaHCO_3$ (1 mL) and diluted with dichloromethane (30 mL). The organic layer was stirred with aqueous NH_4Cl (10 mL) for 10 min. The layers were separated, and the aqueous layer was extracted twice with dichloromethane (20 mL). The combined organic layer were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The resulting crude residue was purified by column chromatography on silica gel (12 % ethyl acetate in hexane) to give 91.1 mg (55 %) of the titled compound as pale yellow syrup. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.25 (m, 4H), 7.20–7.17 (m, 6H), 7.14–7.12 (m, 1H), 7.08 (d, 2H, $J = 8.8$ Hz), 6.81 (d, 2H, $J = 8.8$ Hz), 4.31 (bs, 1H), 4.20–4.13 (m, 2H), 4.05 (d, 1H, $J = 10.2$ Hz), 3.73 (s, 3H), 3.60 (d, 1H, $J = 10.2$ Hz), 3.56 (dd, 1H, $J = 8.8$, 6.4 Hz), 3.44 (dd, 1H, $J = 8.8$, 6.4 Hz), 1.36 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.15, 144.31, 143.48, 132.92, 129.91, 128.44, 128.66, 128.35, 128.29, 127.48, 126.40, 114.33, 110.38, 85.82, 79.39, 77.86, 76.11, 66.23, 55.47, 26.97, 25.75; IR (NaCl, neat): cm^{-1} 3446, 3032, 2986, 1512, 1490, 1448, 1243; $[\alpha]_D^{23}$ +14.3 (*c* 2.23, $CHCl_3$,); HPLC (chiralcel OD column) eluent, 0.25 % i-PrOH/hexane; flow rate, 0.8 mL/min; detection 254 nm light; t_R of (*R*)-major 65.5 min; t_R of (*S*)-minor 62.2 min (major:minor = 80:1, 97 % de); LRMS (FAB) calcd. for $[M+Na]^+$: LRMS (FAB): m/z (relative intensity) 491 ($[M+Na]^+$, 1 %); HRMS (FAB) calcd. for $C_{27}H_{29}ClO_5Na$ 491.1601, found 491.1602.

(*R*)-1-(4-Chlorophenyl)-1-phenylethane-1,2-diol (13)

To the solution of **12** (56 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) were added $SnCl_2$ (5 mg) and EtSH (30 mg, 0.48 mmol). The reaction mixture was stirred at room temperature for 1 h before it was diluted with ethyl acetate (20 mL). The organic layer was washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The resulting crude residue was purified by column chromatography on silica gel (20 % ethyl acetate in hexane) to give the title compound **13** as a white solid (15.8 mg, 53 %): mp 84–86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.19 (m, 9H), 4.09 (d, 1H, $J = 11.4$ Hz), 4.02 (d, 1H, $J = 11.4$ Hz), 3.16 (bs, 1H), 1.84 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.35, 142.38, 133.19, 128.44, 128.38, 127.88, 127.56, 126.25, 78.17, 68.89; IR (KBr, disc): cm^{-1} 3371, 3295, 3057, 2925, 1489, 1210; HPLC analysis: CHIRALCEL OD column, eluent = 5 % isopropanol in hexane, flow rate = 0.5 mL/min, minor (*S* form) $t_R = 49.7$ min, major (*R* form) $t_R = 57.1$ min, minor/major = 1/80 (97 % ee); $[\alpha]_D^{26}$ −8.3 (*c* 1.63, $CHCl_3$); LRMS(FAB) m/z (relative intensity) 271 (M^++Na, 4 %), [213 (M^+–OH, 31 %), 197 (M^+–OHCl, 25 %], 154 (100 %).

(R)-2-(4-Chlorophenyl)-2-hydroxy-2-phenylethyl methanesulfonate (14)

To the solution of diol **13** (43.7 mg, 0.18 mmol) in pyridine (3 mL) was added dropwise methanesulfonyl chloride (72 μL, 0.88 mmol) at 0 °C. After being stirred for 2 h, the reaction mixture was quenched with water (5 mL) and diluted with dichloromethane (30 mL). The organic layer was washed with aqueous $CuSO_4$ and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The resulting crude residue was purified by column chromatography on silica gel (15 % ethyl acetate in hexane) to give the title compound **14** as a white solid (54.1 mg, 94 %): mp 108–110 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 9H), 4.67 (d, $J = 10.8$ Hz, 1H), 4.64 (d, $J = 10.8$ Hz, 1H), 3.33 (brs, 1H), 2.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 140.9, 133.9, 128.6, 128.2, 127.9, 126.3, 76.9, 73.9, 37.5; IR (KBr, disc): cm^{-1} 3479, 3032, 2937,1490, 1357; LRMS(FAB) m/z (relative intensity) 349 (M^++Na, 7 %), 309 (M^+–OH, 58 %), 275 (M^+–OHCl, 23 %), 231 (M^+–CH_3SO_3, 47 %) 154 (100 %).

(*R*)-1-(4-Chlorophenyl)-1-phenylethanol (2)

To the solution of mesylate **14** (45 mg, 0.14 mmol) in THF (3 mL) at 0 °C was added dropwise lithium triethylborohydride (0.55 mL, 1.0 M solution in THF, 0.55 mmol) via syringe. The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with aqueous NH_4Cl

(10 mL) and diluted with ethyl acetate (50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The resulting crude residue was purified by column chromatography on silica gel (11 % ethyl acetate in hexane) to give the title compound as an oil (28 mg, 87 %): $[\alpha]_D^{25}$ −12.1 (*c* 1.0, $CHCl_3$), {$[\alpha]_D^{22}$ −11.2 (*c* 1.9, $CHCl_3$, 92 % ee for (*R*)-isomer) (Stymiest et al. 2008)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.24 (m, 9H), 2.30 (brs, 1H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 146.6, 132.7, 128.3, 128.2, 127.3, 127.2, 125.8, 75.9, 30.8; IR (KBr, disc): cm^{-1} 3413, 1950, 1491, 1371, 1190, 778; LRMS (FAB): m/z (relative intensity) 215 (M^+–OH, 3 %), 181 (M^+–OHCl, 100 %).

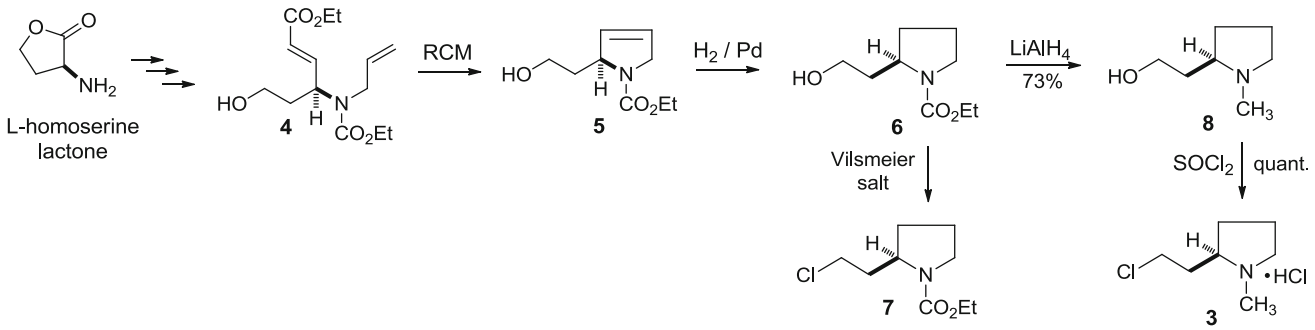
(*R*)-2-(2-((*R*)-1-(4-Chlorophenyl)-1-phenylethoxy)ethyl)-1-methylpyrrolidine (1)

To a suspension of sodium hydride (60 % dispersion in mineral oil, 125 mg, 5.2 mmol) in xylene (20 mL) was added the solution of alcohol **2** (241.3 mg, 1.04 mmol) in xylene (2 mL) to at room temperature, followed by stirring for 10 min. Then a solution of (*R*)-2-(2-chloroethyl)-1-methylpyrrolidine (**3**, 122.5 mg, 0.83 mmol) in xylene (3 mL) was added and the mixture was refluxed at 140 °C for 4 h. The reaction mixture was quenched with water (10 mL) and diluted with ethyl acetate (50 mL). The layers were separated, and the aqueous layer was extracted twice with ethyl acetate (10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The resulting crude residue was purified by column chromatography on silica gel (a 1:1 mixture of ethyl acetate and methanol) to give the (*R*,*R*)-clemastine (**1**) as a pale yellow oil (55 mg, 21.3 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 9H), 3.26 (m, 2H), 3.04 (m, 1H), 2.31 (s, 3H), 2.11 (m, 2H), 2.02 (m, 1H), 1.87 (m, 1H), 1.82 (s, 3H), 1.72 (m, 2H), 1.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1, 145.7, 132.4, 128.04, 128.01, 127.9, 126.9, 126.6, 79.9, 63.7, 60.4, 57.1, 40.4, 34.5, 30.9, 25.5, 21.8; IR (NaCl, neat): cm^{-1} 2940, 2872, 2774, 1488, 1446, 1211, 1092; $[\alpha]_D^{27}$ +31.7 (*c* 1.04, EtOH){$[\alpha]_D^{20}$ +33.7 for (*R*)-isomer (Ebnöther and Weber 1976), $[\alpha]_D^{20}$ −37.4 for (*S*)-isomer (Fournier et al. 2010)}; LRMS (CI): m/z (relative intensity) 344 ($[M+H]^+$, 42 %), HRMS (CI): calcd for $C_{21}H_{27}ClNO$ $[M+H]^+$: 344.1781, found 344.1783.

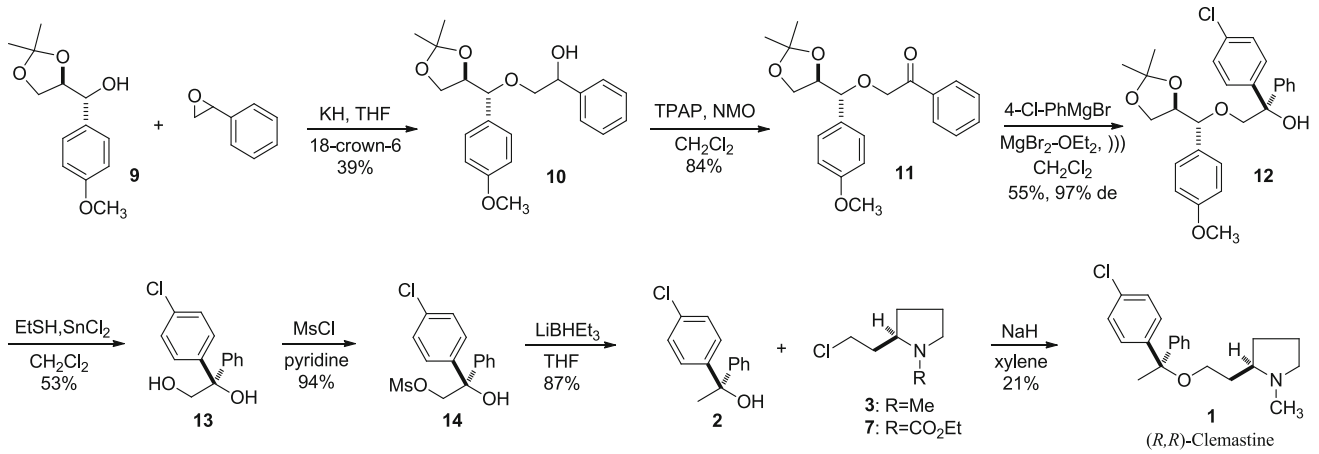
Results and discussion

Our synthetic strategy for (*R*,*R*)-clemastine (**1**) was based on the approaches outlined in Schemes 1 and 2, which involve the preparations and coupling of two components: (*R*)-tertiary alcohol **2** and (*R*)-chloroethylpyrrolidine **3**. (*R*)-Tertiary alcohol **2** was synthesized using our recently reported chelation-controlled asymmetric alkylation process (Kim et al. 2014). Having (*R*)-configuration, **3** could not be accessible from natural (*S*)-proline. We need to develop a novel synthetic method for **3** with (*R*)-configuration. Recently, we also reported on the preparation of the carbamate **6** and **7** starting with L-homoserine lactone, which involves racemization-minimized *N*-allylation and ring-closing metathesis (RCM) as shown in Scheme 1 (Kim et al. 2011). Thus, (*R*)-2-chloroethylpyrrolidine **3** could be made from carbamate **6** in a two-step process involving reduction and chlorination. $LiAlH_4$ reduction of **6** in THF at room temperature reduced the carbamate group, producing the (*R*)-*N*-methyl-2-hydroxyethylpyrrolidine derivative **8** in 73 % yield. The alcohol was converted to the corresponding chloride **3** with thionyl chloride in chloroform at refluxing temperature, which returned the amine hydrochloride salt (*R*)-**3**·HCl in quantitative yield.

The tertiary alcohol (*R*)-**2** was made from the corresponding diol **13**, outlined in Scheme 2, which is readily accessible from the chiral auxiliary **9** developed by us. (Jung et al. 2000) Chiral benzyl alcohol **9**, directly prepared from (*R*)-glyceraldehyde diacetonide, was converted to the corresponding alkoxide with KH in tetrahydrofuran, followed by *O*-alkylation with styrene oxide in the presence of 18-crown-6 ether to afford **10** in 39 % yield (Sato et al.



Scheme 1 Synthetic route to (*R*)-chloroethylpyrrolidine 3



Scheme 2 Synthetic route to (*R*)-tertiary alcohol **2** and (*R*,*R*)-clemastine (**1**)

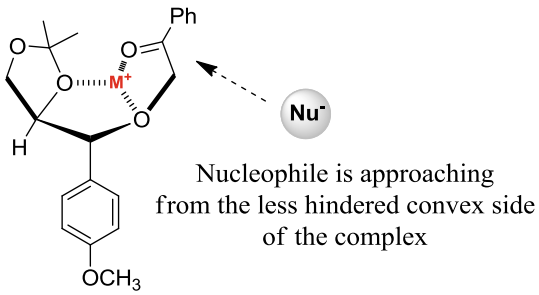


Fig. 2 Hypothetical chelated transition state

1985). TPAP oxidation of the resulting alcohol **10** was accomplished in the presence of *N*-methylmorpholine-*N*-oxide, giving ketone **11** in 84 % yield. Then, we undertook the chelation-controlled asymmetric nucleophilic 1,2-addition as a key reaction. Performing the nucleophilic addition of 4-chlorophenylmagnesium bromide to phenyl ketone **11**, pre-complexed with $MgBr_2$·etherate in CH_2Cl_2 at −78 °C, followed by hydrolysis gave **12** in 55 % chemical yield. Optical purity was measured by HPLC analysis using chiral column, proved to be 97 % de. The absolute configuration of the newly created stereogenic center on **12** could not be rigorously established at the present stage, but was assigned tentatively as (*R*) on the basis of our proposed chelation model as shown in Fig. 2. The preferential formation of (*R*)-**12** over (*S*)-**12** and the high level of stereoselectivity associated with the asymmetric induction may be explained by considering the following hypothetical transition state model of the complex, resulted from tridentate chelation of the internal three oxygens with magnesium ion. In the model, the 5-membered chelated structure containing a carbonyl group is puckered upside, minimizing the steric repulsion with the nearby aryl ring. Therefore, nucleophile is approaching from the less hindered side of the complex, *syn* to the aromatic ring. The subsequent transformation of **12** to (*R*,*R*)-clemastine is straightforward. By treating **12** with EtSH and $SnCl_2$ in dichloromethane, chiral benzyl group was removed to produce the diol **13** in 53 % yield. At this stage, the enantiomeric purity of the **12** was reconfirmed by analyzing the diol **13** by chiral HPLC (Chiralcel OD column). As chiral diols are readily available from the corresponding alkenes by Sharpless asymmetric dihydroxylation (Vanhessche and Sharpless 1996), we and others also prepared the diol **13** from 1-chloro-4-(1-phenylvinyl)benzene using AD-mix-β as a chiral catalyst. However, the enantioselectivity was very low (25–29 % ee), implying that Sharpless AD method is not satisfactory to discriminate the small difference between phenyl and 4-chlorophenyl group around the double bond. At the stage, absolute configuration of **13** could be confirmed as (*R*) based on the X-ray analysis reported by Han et al. (2011). Selective mesylation of diol **13** with methanesulfonyl chloride in pyridine produced mesylate **14** in 94 % yield. Lithium triethylborohydride reduction of mesylate **14** in THF produced tertiary alcohol **2** in good yield. Absolute configuration of **2** was reconfirmed as (*R*) by comparison with literature data (Forrat et al. 2006; Stymiest et al. 2008; Fernández-Mateos et al. 2014; Shimizu et al. 2015).

Now, both (*R*)-tertiary alcohol **2** and (*R*)-chloroethylpyrrolidine **3** were prepared for the final stage of the synthesis. Final couplings of **2** and **3** under basic conditions were well-documented, but suffered from low yields due to steric hindrance of **2**. Thus, at first, we chose carbamate **7** as amine partner for the coupling reaction with **2**. However, our initial attempts using carbamate **7** were found to be unsuccessful, suggesting that formation of a more reactive intermediate from **3** seems to be necessary for the coupling reaction to occur. When the nitrogen is nucleophilic enough, a bicyclic cation (1-methyl-1-azabicyclo[3.2.0]heptan-1-ium) is expected to be formed from **3** via an intramolecular S_N2 reaction. For coupling reaction with **2**, amine partner should be **3**, and not neutral

carbamate **7**. Thus, we carried out the final coupling reaction of **2** and **3** via *O*-alkylation, and completed the asymmetric synthesis of (*R*,*R*)-clemastine (**1**) for the first time. The synthetic **1** was identical in all respect (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$) to those obtained from optical resolution method report by Ebnöther and Weber (1976).

In summary, the first asymmetric synthesis of (*R*,*R*)-clemastine (**1**) has been accomplished by coupling (*R*)-tertiary alcohol **2** and (*R*)-chloroethylpyrrolidine **3** via *O*-alkylation. (*R*)-Tertiary alcohol **2** can be prepared efficiently from our chiral auxiliary through a stereoselective alkylation. A high degree of 1,4-asymmetric induction (up to 97 % de) has been realized during alkylation step via a chelation-controlled mechanism. In the reaction, chiral benzyl group acts as a chiral auxiliary as well as a protecting group. (*R*)-Chloroethylpyrrolidine **3** was prepared by asymmetric transformation starting with L-homoserine lactone, with racemization-minimized *N*-allylation and ring-closing metathesis involved as key steps.

Acknowledgments This research was supported by the Sookmyung Women's University Research Grants 2012.

Compliance with ethical standards

Conflict of interest All authors declare that there is no conflict of interest with any financial, personal or other relationships with other people or organizations that could inappropriately influence or be perceived to influence this study.

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